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DIALOG(R)File 345:Inpadoc/Fam.& Legal Stat

13844934
Basic Patent (No,Kind,Date): EP 309297 A2 19890329 <No. of Patents: 119>

PATENT FAMILY:
AUSTRIA (AT)
Patent (No,Kind,Date): AT 100465 E 19940215
ANALOGE VON BRADYKININ, DESSEN SYNTHESE UND DESSEN BENUTZUNG IN DER THERAPIE. (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E
Priority (No,Kind,Date): EP 89303065 A 19890328; US 173311 A 19880325
Applic (No,Kind,Date): EP 89303065 A 19890328
Addnl Info: 00334685 19940119
IPC: * C07K-007/00; A61K-037/02
CA Abstract No: * 112(17)158978R; 112(19)179890W
Derwent WPI Acc No: * C 89-280003; C 89-309505
Language of Document: English
Patent (No,Kind,Date): AT 113961 E 19941115
THERAPEUTISCHE PEPTIDE. (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924
Applic (No,Kind,Date): EP 88308916 A 19880926
Addnl Info: 00309297 19941109
IPC: * C07K-007/00; A61K-037/02; C07K-007/02
CA Abstract No: * 111(11)097733N
Derwent WPI Acc No: * C 89-095447
Language of Document: German
Patent (No,Kind,Date): AT 139540 E 19960715
HEILMITTELPEPTIDE (German)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): EP 90913117 A 19900817
Addnl Info: 00489089 19960619
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: German
Patent (No,Kind,Date): AT 143372 E 19961015
SUBSTANCE P ANTAGONISTE (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): EP 90912128 A 19900816
Addnl Info: 00438566 19960925
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: German
Patent (No,Kind,Date): AT 165836 E 19980515
PEPTIDE ALS ARZNEIMITTEL (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): EP 89912292 A 19891013

Addnl Info: 00438519 19980506
IPC: * C07K-007/02; C07K-014/595; A61K-038/16
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K; 123(21)286737A; 128(18)213739W
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241; C 95-169633
Language of Document: German

AUSTRALIA (AU)
Patent (No,Kind,Date): AU 8827102 A1 19890418
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): WO 88US3286 A 19880923; US 100571 A 19870924
Applic (No,Kind,Date): AU 8827102 A 19880923
IPC: * C07K-007/02; C07K-007/06; C07K-007/08
Derwent WPI Acc No: * C 89-095447
Language of Document: English
Patent (No,Kind,Date): AU 8934146 A1 19891016
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): WO 89US1259 A 19890327; US 173311 A 19880325; US 282328 A 19881209
Applic (No,Kind,Date): AU 8934146 A 19890327
IPC: * C07K-007/18
Language of Document: English
Patent (No,Kind,Date): AU 8934280 A1 19891016
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E
Priority (No,Kind,Date): WO 89US1216 A 19890322; US 173311 A 19880325
Applic (No,Kind,Date): AU 8934280 A 19890322
IPC: * C07K-007/18
Language of Document: English
Patent (No,Kind,Date): AU 8944949 A1 19900501
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): WO 89US4616 A 19891013; US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): AU 8944949 A 19891013
IPC: * C07K-007/02; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
Derwent WPI Acc No: * C 89-309505
Language of Document: English
Patent (No,Kind,Date): AU 9061231 A1 19910228
TWO-SIDED PLAYING PIECE GAME SET (English)
Patent Assignee: LAMLE STEWART M
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): AU 9061231 A 19900822
IPC: * A63F-009/20; A63F-001/02
Language of Document: English
Patent (No,Kind,Date): AU 9062940 A1 19910403
THERAPEUTIC PEPTIDES (English)
Patent Assignee: BIOMEASURE INC
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; KIM SUN HYUK
Priority (No,Kind,Date): WO 90US4646 A 19900817; US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): AU 9062940 A 19900817
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: * 113(19)172755T
Derwent WPI Acc No: * C 90-147822

Language of Document: English
Patent (No,Kind,Date): AU 9514808 A1 19960926
BOMBESIN ANALOGS (English)
Patent Assignee: BIOMEASURE INC
Author (Inventor): KIM SUN HYUK; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): AU 9514808 A 19950313; US 337127 A 19941110
Applic (No,Kind,Date): AU 9514808 A 19950313
IPC: * C07K-007/02; A61K-038/08
CA Abstract No: * 128(18)213739W
Derwent WPI Acc No: * C 96-455920; C 98-229235; C 99-189718; C 96-455920
Language of Document: English
Patent (No,Kind,Date): AU 622123 B2 19920402
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): WO 88US3286 A 19880923; US 100571 A 19870924
Applic (No,Kind,Date): AU 8827102 A 19880923
IPC: * A61K-037/02; C07K-007/06; C07K-007/08
CA Abstract No: * 111(11)097733N
Derwent WPI Acc No: * C 89-095447
Language of Document: English
Patent (No,Kind,Date): AU 624566 B2 19920611
TWO-SIDED PLAYING PIECE GAME SET (English)
Patent Assignee: LAMLE STEWART M
Author (Inventor): LAMLE STEWART M
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): AU 9061231 A 19900822
IPC: * G06F-015/44; A63F-009/20; A63F-001/02
Derwent WPI Acc No: * G 91-059703
Language of Document: English
Patent (No,Kind,Date): AU 638423 B2 19930701
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): WO 89US4616 A 19891013; US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): AU 8944949 A 19891013
IPC: * C07K-007/02; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: English
Patent (No,Kind,Date): AU 648037 B2 19940414
THERAPEUTIC PEPTIDES (English)
Patent Assignee: BIOMEASURE INC
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; KIM SUN HYUK
Priority (No,Kind,Date): WO 90US4646 A 19900817; US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): AU 9062940 A 19900817
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02 ; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30; A61K-037/02
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: English
Patent (No,Kind,Date): AU 703865 B2 19990401
BOMBESIN ANALOGS (English)
Patent Assignee: BIOMEASURE INC
Author (Inventor): KIM SUN HYUK; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): AU 9514808 A 19950313
Applic (No,Kind,Date): AU 9514808 A 19950313
IPC: * C07K-007/02; A61K-038/08
Derwent WPI Acc No: * C 96-455920
Language of Document: English

CANADA (CA)
Patent (No,Kind,Date): CA 2008454 AA 19900902
THERAPEUTIC PEPTIDES (English; French)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES P (US); TAYLOR JOHN E (US); KIM SUN H (US)
Priority (No,Kind,Date): US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): CA 2008454 A 19900124
National Class: * D3530000706 M; 16701038 S
IPC: * C07K-007/06; A61K-037/02
CA Abstract No: * 113(19)172755T
Derwent WPI Acc No: * C 90-147822
Language of Document: English

Patent (No,Kind,Date): CA 2023460 AA 19910224
TWO-SIDED PLAYING PIECE GAME SET (English; French)
Patent Assignee: LAMLE STEWART M (US)
Author (Inventor): LAMLE STEWART M (US)
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): CA 2023460 A 19900816
National Class: * D42720065 M
IPC: * A63F-009/20
Language of Document: English

Patent (No,Kind,Date): CA 2039175 AA 19910217
THERAPEUTIC PEPTIDES (English; French)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): CA 2039175 A 19900816
National Class: * D2530000708 M; 530000506 S; 530000502 S; 530000706 S; 530000702 S; 530000510 S; 530000508 S
IPC: * C07K-007/08; C07K-007/06; C07K-007/02; C07K-005/00
CA Abstract No: * 115(15)151906U
Derwent WPI Acc No: * C 91-087240
Language of Document: English

Patent (No,Kind,Date): CA 2064896 AA 19910222
THERAPEUTIC PEPTIDES (English; French)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN H (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): CA 2064896 A 19900817
IPC: * C07K-007/06; C07K-007/00; C07K-005/00; C07K-007/30
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: English

Patent (No,Kind,Date): CA 1335622 A1 19950516
BRADYKININ ANALOGS CONTAINING A NON-PEPTIDE BOND (English; French)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US)
Priority (No,Kind,Date): US 173311 A 19880325
Applic (No,Kind,Date): CA 594845 A 19890328
National Class: * D1530000718 M; 167010346 S
IPC: * C07K-007/18; A61K-037/42; A61K-037/43
CA Abstract No: * 112(17)158978R; 112(19)179890W; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-280003; C 89-309505; C 95-169633; C 98-229235; C 98-296827; C 99-189718
Language of Document: English

CZECH REPUBLIC (CZ)
Patent (No,Kind,Date): CZ 9004028 A3 19990414
LINEAR PEPTIDE (Czech; English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816

Applic (No,Kind,Date): CZ 904028 A 19900816
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Czech; Slovak
Patent (No,Kind,Date): CZ 285319 B6 19990714
LINEAR PEPTIDE (Czech; English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): CZ 904028 A 19900816
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Czech; Slovak
Patent (No,Kind,Date): CZ 285562 B6 19990915
LINEAR PEPTIDE (Czech; English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): CZ 99774 A 19900816
IPC: * C07K-007/02; C07K-007/22
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Czech; Slovak

GERMAN DEMOCRATIC REPUBLIC (DD)
Patent (No,Kind,Date): DD 298411 A5 19920220
THERAPEUTISCHE PEPTIDE (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): DD 343501 A 19900816
IPC: * C07K-007/06; A61K-037/02; C07K-007/02
CA Abstract No: * 115(15)151906U
Derwent WPI Acc No: * C 91-087240
Language of Document: German

GERMANY (DE)
Patent (No,Kind,Date): DE 3852086 C0 19941215
THERAPEUTISCHE PEPTIDE. (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924
Applic (No,Kind,Date): DE 3852086 A 19880926
IPC: * C07K-007/00; A61K-037/02; C07K-007/02
CA Abstract No: * 111(11)097733N
Derwent WPI Acc No: * C 89-095447
Language of Document: German
Patent (No,Kind,Date): DE 68912376 C0 19940303
ANALOGE VON BRADYKININ, DESSEN SYNTHESE UND DESSEN BENUTZUNG IN DER THERAPIE. (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US)
Priority (No,Kind,Date): US 173311 A 19880325
Applic (No,Kind,Date): EP 89303065 A 19890328
IPC: * C07K-007/00; A61K-037/02
CA Abstract No: * 112(17)158978R; 112(19)179890W
Derwent WPI Acc No: * C 89-280003; C 89-309505
Language of Document: German
Patent (No,Kind,Date): DE 68928667 C0 19980610
PEPTIDE ALS ARZNEIMITTEL (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN (US); KIM SUN (US)
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169

A 19890821; WO 89US4616 W 19891013
Applic (No,Kind,Date): DE 68928667 A 19891013
IPC: * C07K-007/02; C07K-014/595; A61K-038/16
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K; 123(21)286737A; 128(18)213739W
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241; C 95-169633; C 98-229235
Language of Document: German

Patent (No,Kind,Date): DE 69027533 C0 19960725
HEILMITTELPEPTIDE (German)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID (US); MOREAU JACQUES-PIERRE (US); KIM SUN (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330; WO 90US4646 W 19900817
Applic (No,Kind,Date): DE 69027533 A 19900817
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: German

Patent (No,Kind,Date): DE 69028692 C0 19961031
SUBSTANCE P ANTAGONISTE (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816; WO 90US4633 W 19900816
Applic (No,Kind,Date): DE 69028692 A 19900816
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: German

Patent (No,Kind,Date): DE 3852086 T2 19950518
THERAPEUTISCHE PEPTIDE. (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924
Applic (No,Kind,Date): DE 3852086 A 19880926
IPC: * C07K-007/00; A61K-038/00; C07K-007/02
CA Abstract No: * 111(11)097733N
Derwent WPI Acc No: * C 89-095447
Language of Document: German

Patent (No,Kind,Date): DE 68912376 T2 19940707
ANALOGE VON BRADYKININ, DESSEN SYNTHESE UND DESSEN BENUTZUNG IN DER THERAPIE. (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US)
Priority (No,Kind,Date): US 173311 A 19880325
Applic (No,Kind,Date): DE 68912376 A 19890328
IPC: * C07K-007/00; A61K-037/02
CA Abstract No: * 112(17)158978R; 112(19)179890W
Derwent WPI Acc No: * C 89-280003; C 89-309505
Language of Document: German

Patent (No,Kind,Date): DE 68928667 T2 19981001
PEPTIDE ALS ARZNEIMITTEL (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN (US); KIM SUN (US)
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821; WO 89US4616 W 19891013
Applic (No,Kind,Date): DE 68928667 A 19891013
IPC: * C07K-007/02; C07K-014/595; A61K-038/16
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241; C 95-169633; C 98-229235; C 98-296827
Language of Document: German

Patent (No,Kind,Date): DE 69027533 T2 19961219
HEILMITTELPEPTIDE (German)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID (US); MOREAU JACQUES-PIERRE (US); KIM SUN (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330; WO 90US4646 W 19900817
Applic (No,Kind,Date): DE 69027533 A 19900817
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: German
Patent (No,Kind,Date): DE 69028692 T2 19970220
SUBSTANCE P ANTAGONISTE (German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816; WO 90US4633 W 19900816
Applic (No,Kind,Date): DE 69028692 A 19900816
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: German

DENMARK (DK)
Patent (No,Kind,Date): DK 9100663 A 19910614
TERAPEUTISK VIRKSOMME PEPTIDER (Danish)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821; WO 89US4616 A 19891013
Applic (No,Kind,Date): DK 91663 A 19910412
IPC: * C07K-007/30
CA Abstract No: * 112(17)158978R; 113(19)172755T
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: Danish
Patent (No,Kind,Date): DK 8902494 A 19890720
THERAPEUTISK VIRKSOMME PEPTIDER, ISAER BOMBESINANTAGONISTISKE OG LITORINANTAGONISTISKE PEPTIDER SAMT FREMGANGSMAADE TIL FREMSTILLING DERAF (Danish)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 A 19880923
Applic (No,Kind,Date): DK 892494 A 19890523
IPC: * C07K-007/08
CA Abstract No: * 111(11)097733N
Derwent WPI Acc No: * C 89-095447
Language of Document: Danish
Patent (No,Kind,Date): DK 9100663 A0 19910412
TERAPEUTISK VIRKSOMME PEPTIDER (Danish)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821; WO 89US4616 A 19891013
Applic (No,Kind,Date): DK 91663 A 19910412
IPC: * C07K-007/30
CA Abstract No: * 112(17)158978R; 113(19)172755T
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: Danish
Patent (No,Kind,Date): DK 8902494 A0 19890523
THERAPEUTISK VIRKSOMME PEPTIDER, ISAER BOMBESINANTAGONISTISKE OG LITORINANTAGONISTISKE PEPTIDER SAMT FREMGANGSMAADE TIL FREMSTILLING DERAF (Danish)

Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 A 19880923
Applic (No,Kind,Date): DK 892494 A 19890523
IPC: * C07K-007/08
Derwent WPI Acc No: * C 89-095447
Language of Document: Danish

Patent (No,Kind,Date): DK 438566 T3 19961111
SUBSTANS P-ANTAGONISTER (Danish)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): DK 9090912128 A 19900816
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02 ; C07K-007/06; C07K-007/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Danish

Patent (No,Kind,Date): DK 489089 T3 19960729
TERAPEUTISKE PEPTIDER (Danish)
Patent Assignee: UNIV TULANE (US); BIOMEASURE INC (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): DK 9090913117 A 19900817
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02 ; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: * 113(19)172755T; 115(15)150377K; 128(18)213739W
Derwent WPI Acc No: * C 90-147822; C 91-087241; C 98-229235
Language of Document: Danish

EUROPEAN PATENT OFFICE (EP)

Patent (No,Kind,Date): EP 414512 A1 19910227
TWO-SIDED PLAYING PIECE GAME SET (English; French; German)
Patent Assignee: LAMLE STEWART M (US)
Author (Inventor): LAMLE STEWART M (US)
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): EP 90309187 A 19900822
Designated States: (National) AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE
IPC: * A63F-009/20
Derwent WPI Acc No: ; G 91-059703
Language of Document: English

Patent (No,Kind,Date): EP 438519 A1 19910731
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): WO 89US4616 W 19891013; US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): EP 89912292 A 19891013
Designated States: (National) AT; BE; CH; DE; FR; GB; IT; LI; LU; NL; SE
IPC: * C07K-007/02; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: * 112(17)158978R; 113(19)172755T
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: English

Patent (No,Kind,Date): EP 438566 A1 19910731
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): WO 90US4633 W 19900816; US 394727 A 19890816
Applic (No,Kind,Date): EP 90912128 A 19900816
Designated States: (National) AT; BE; CH; DE; DK; ES; FR; GB; IT; LI;

LU; NL; SE
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02 ; C07K-007/06; C07K-007/08
Derwent WPI Acc No: * C 91-087240
Language of Document: English

Patent (No,Kind,Date): EP 489089 A1 19920610
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): WO 90US4646 W 19900817; US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): EP 90913117 A 19900817
Designated States: (National) AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02 ; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: English

Patent (No,Kind,Date): EP 309297 A2 19890329
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 100571 A 19870924
Applic (No,Kind,Date): EP 88308916 A 19880926
Designated States: (National) AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
IPC: * C07K-007/00; A61K-037/02
CA Abstract No: ; 111(11)097733N
Derwent WPI Acc No: ; C 89-095447
Language of Document: English

Patent (No,Kind,Date): EP 334685 A2 19890927
BRADYKININ ANALOGUES, THEIR SYNTHESIS AND THEIR USE IN THERAPY (English ; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E
Priority (No,Kind,Date): US 173311 A 19880325
Applic (No,Kind,Date): EP 89303065 A 19890328
Designated States: (National) AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
IPC: * C07K-007/00; A61K-037/02
CA Abstract No: ; 112(19)179890W
Derwent WPI Acc No: ; C 89-280003
Language of Document: English

Patent (No,Kind,Date): EP 309297 A3 19900704
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 100571 A 19870924
Applic (No,Kind,Date): EP 88308916 A 19880926
Designated States: (National) AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
IPC: * C07K-007/00; A61K-037/02; C07K-007/02
CA Abstract No: * 111(11)097733N
Derwent WPI Acc No: * C 89-095447
Language of Document: English

Patent (No,Kind,Date): EP 334685 A3 19910130
BRADYKININ ANALOGUES, THEIR SYNTHESIS AND THEIR USE IN THERAPY (English ; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E
Priority (No,Kind,Date): US 173311 A 19880325
Applic (No,Kind,Date): EP 89303065 A 19890328
Designated States: (National) AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
IPC: * C07K-007/00; A61K-037/02
CA Abstract No: * 112(17)158978R; 112(19)179890W

Derwent WPI Acc No: * C 89-280003; C 89-309505
Language of Document: English

Patent (No,Kind,Date): EP 438519 A4 19911030
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): WO 89US4616 W 19891013; US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): EP 89912292 A 19891013
Designated States: (National) AT; BE; CH; DE; FR; GB; IT; LI; LU; NL; SE
IPC: * C07K-007/02; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: * 112(17)158978R; 113(19)172755T
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: English

Patent (No,Kind,Date): EP 438566 A4 19930331
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): WO 90US4633 W 19900816; US 394727 A 19890816
Applic (No,Kind,Date): EP 90912128 A 19900816
Designated States: (National) AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02 ; C07K-007/06; C07K-007/08
CA Abstract No: * 115(15)151906U
Derwent WPI Acc No: * C 91-087240
Language of Document: English

Patent (No,Kind,Date): EP 489089 A4 19920624
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): WO 90US4646 W 19900817; US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): EP 90913117 A 19900817
Designated States: (National) AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02 ; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: English

Patent (No,Kind,Date): EP 309297 B1 19941109
THERAPEUTIC PEPTIDES. (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924
Applic (No,Kind,Date): EP 88308916 A 19880926
Designated States: (National) AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
IPC: * C07K-007/00; A61K-037/02; C07K-007/02
CA Abstract No: * 111(11)097733N; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-095447; C 95-169633; C 98-229235; C 98-296827; C 99-189718
Language of Document: English

Patent (No,Kind,Date): EP 334685 B1 19940119
BRADYKININ ANALOGUES, THEIR SYNTHESIS AND THEIR USE IN THERAPY (English ; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US)
Priority (No,Kind,Date): US 173311 A 19880325
Applic (No,Kind,Date): EP 89303065 A 19890328

Designated States: (National) AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
IPC: * C07K-007/00; A61K-037/02
CA Abstract No: * 112(17)158978R; 112(19)179890W
Derwent WPI Acc No: * C 89-280003; C 89-309505
Language of Document: English

Patent (No,Kind,Date): EP 438519 B1 19980506
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821; WO 89US4616 W 19891013
Applic (No,Kind,Date): EP 89912292 A 19891013
Designated States: (National) AT; BE; CH; DE; FR; GB; IT; LI; LU; NL; SE
IPC: * C07K-007/02; C07K-014/595; A61K-038/16
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K; 123(21)286737A; 128(18)213739W
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241; C 95-169633
Language of Document: English

Patent (No,Kind,Date): EP 438566 B1 19960925
SUBSTANCE P ANTAGONISTS (English; French; German)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816; WO 90US4633 W 19900816
Applic (No,Kind,Date): EP 90912128 A 19900816
Designated States: (National) AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: English

Patent (No,Kind,Date): EP 489089 B1 19960619
THERAPEUTIC PEPTIDES (English; French; German)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): WO 90US4646 W 19900817; US 502438 A 19900330; US 397169 A 19890821
Applic (No,Kind,Date): EP 90913117 A 19900817
Designated States: (National) AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: English

SPAIN (ES)

Patent (No,Kind,Date): ES 2061977 T3 19941216
COMPUESTOS ANALOGOS A BRADIQUININA, SU SINTESIS Y SU USO EN TERAPIA. (Spanish)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US)
Priority (No,Kind,Date): US 173311 A 19880325
Applic (No,Kind,Date): ES 89303065 EP 19890328
Addnl Info: 0334685 EP patent valid in AT
IPC: * C07K-007/00; A61K-037/02
CA Abstract No: * 112(17)158978R; 112(19)179890W
Derwent WPI Acc No: * C 89-280003; C 89-309505
Language of Document: Spanish

Patent (No,Kind,Date): ES 2065336 T3 19950216
PEPTIDOS TERAPEUTICOS. (Spanish)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)

Priority (No,Kind,Date): US 100571 A 19870924
Applic (No,Kind,Date): ES 88308916 EP 19880926
Addnl Info: 0309297 EP patent valid in AT
IPC: * C07K-007/00; A61K-037/02; C07K-007/02
CA Abstract No: * 111(11)097733N
Derwent WPI Acc No: * C 89-095447
Language of Document: Spanish

Patent (No,Kind,Date): ES 2090140 T3 19961016
PEPTIDOS TERAPEUTICOS. (Spanish)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): ES 90913117 EP 19900817
Addnl Info: 0489089 EP patent valid in AT
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: Spanish

Patent (No,Kind,Date): ES 2094160 T3 19970116
PEPTIDOS TERAPEUTICOS, EN PARTICULAR ANALOGOS DEL PEPTIDO SUBSTANCIA P. (Spanish)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): ES 90912128 EP 19900816
Addnl Info: 0438566 EP patent valid in AT
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Spanish

FINLAND (FI)

Patent (No,Kind,Date): FI 8902507 A 19890523
TERAPEUTISKA PEPTIDER. (Swedish)
Patent Assignee: UNIV TULANE (US); COY DAVID HOWARD (US); MOREAU JACQUES PIERRE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 A 19880923
Applic (No,Kind,Date): FI 892507 A 19890523
IPC: * C07K
Derwent WPI Acc No: * C 89-095447
Language of Document: Finnish; Swedish

Patent (No,Kind,Date): FI 8902507 A0 19890523
TERAPEUTISKA PEPTIDER. (Swedish)
Patent Assignee: UNIV TULANE (US); COY DAVID HOWARD (US); MOREAU JACQUES PIERRE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 A 19880923
Applic (No,Kind,Date): FI 892507 A 19890523
IPC: * C07K
Derwent WPI Acc No: * C 89-095447
Language of Document: Finnish; Swedish

Patent (No,Kind,Date): FI 9004153 A0 19900822
DUBBELSIDIGA SPELDELAR OMFATTANDE SPEL. (Swedish)
Patent Assignee: LAMLE STEWART MILTON (US)
Author (Inventor): LAMLE STEWART MILTON (US)
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): FI 904153 A 19900822
IPC: * A63F
Language of Document: Finnish; Swedish

Patent (No,Kind,Date): FI 9101780 A0 19910412
TERAPEUTISKA PEPTIDER. (Swedish)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US);

TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821; WO 89US4616 A 19891013
Applic (No,Kind,Date): FI 911780 A 19910412
IPC: * C07K
CA Abstract No: * 112(17)158978R; 113(19)172755T
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: Finnish; Swedish

Patent (No,Kind,Date): FI 9200737 A0 19920220
TERAPEUTISKA PEPTIDER. (Swedish)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330; WO 90US4646 A 19900817
Applic (No,Kind,Date): FI 92737 A 19920220
IPC: * C07K
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: Finnish; Swedish

Patent (No,Kind,Date): FI 100719 B1 19980213
FOERFARANDE FOER FRAMSTAELLNING AV TERAPEUTISKT ANVAENDBARA, MODIFIERADE BOMBESIN- OCH LITORINANTAGONISTPEPTIDER (Swedish)
Patent Assignee: UNIV TULANE (US); COY DAVID HOWARD (US); MOREAU JACQUES PIERRE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 W 19880923
Applic (No,Kind,Date): FI 892507 A 19890523
IPC: * C07K-007/02; C07K-007/06; C07K-007/08
CA Abstract No: * 111(11)097733N; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-095447; C 95-169633; C 98-229235; C 98-296827
Language of Document: Finnish; Swedish

Patent (No,Kind,Date): FI 104252 B1 19991215
MENETELMAE TERAPEUTTISESTI KAEYTTOEKELPOISTEN PEPTIDIEN KEMIALLISEKSI SYNTETISOIMISEKSI KIINTEAESSAE FAASISSA FOERFARANDE FOER KEMISK SYNTES I FAST FAS AV TERAPEUTISKT ANVAENDBARA PEPTIDER (Swedish)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821; WO 89US4616 W 19891013
Applic (No,Kind,Date): FI 911780 A 19910412
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241; C 95-169633; C 98-229235; C 98-296827; C 99-189718
Language of Document: Finnish; Swedish

GREECE (GR)

Patent (No,Kind,Date): GR 90100613 A 19911230
THERAPEUTICAL PEPTIDES (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): GR 100613 A 19900816
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02; C07K-007/06; C07K-007/08; C07K-007/22
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Greek

HONG KONG (HK)

Patent (No,Kind,Date): HK 1010785 A1 19990625
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821; WO 89US4616 W 19891013
Applic (No,Kind,Date): HK 98111817 A 19981106
IPC: * C07K; A61K
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241; C 95-169633; C 98-229235; C 98-296827; C 99-189718
Language of Document: English

HUNGARY (HU)
Patent (No,Kind,Date): HU 8906391 A0 19910729
PEPTIDES WITH MEDICATIVE EFFECT (English)
Patent Assignee: ADMINISTRATORS OF THE TULANE
Author (Inventor): COY DAVID; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): HU 9163 A 19891013
CA Abstract No: * 112(17)158978R; 113(19)172755T
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: Hungarian
Patent (No,Kind,Date): HU 9006872 A0 19910729
THERAPEUTIC PEPTIDES (English)
Patent Assignee: ADMINISTRATORS OF THE TULANE
Author (Inventor): COY DAVID; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): HU 906872 A 19900816
Derwent WPI Acc No: * C 91-087240
Language of Document: Hungarian
Patent (No,Kind,Date): HU T59420 A2 19920528
PROCESS FOR PRODUCING PEPTIDES HAVING PHARMACEUTICAL ACTION (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): HU 9163 A 19891013
IPC: * C07K-007/02; C07K-007/08; C07K-007/06; C07K-007/10; C07K-007/30
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: Hungarian
Patent (No,Kind,Date): HU T65465 A2 19940628
PROCESS FOR PRODUCING THE RAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): HU 906872 A 19900816
IPC: * C07K-005/02; C07K-005/08; C07K-005/06; C07K-005/10; C07K-007/02; C07K-007/06; C07K-007/08
CA Abstract No: * 115(15)151906U
Derwent WPI Acc No: * C 91-087240
Language of Document: Hungarian
Patent (No,Kind,Date): HU 208439 B 19931028
PROCESS FOR PRODUCING PHARMACEUTICAL PEPTIDES (English)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169

A 19890821
Applic (No,Kind,Date): HU 9163 A 19891013
IPC: * C07K-007/02; C07K-007/08; C07K-007/06; C07K-007/10; C07K-007/30
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: Hungarian

IRELAND (IE)
Patent (No,Kind,Date): IE 91902958 A1 19910227
SUBSTANCE P ANTAGONISTS (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): IE 902958 A 19900815
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: English
Patent (No,Kind,Date): IE 9777033 B 19971119
SUBSTANCE P ANTAGONISTS (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): IE 902958 A 19900815
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: English

JAPAN (JP)
Patent (No,Kind,Date): JP 3141961 A2 19910617
GAME SET HAVING TWO-FACED PIECE (English)
Patent Assignee: SUCHIYUAATO EMU RAMURE
Author (Inventor): SUCHIYUAATO EMU RAMURE
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): JP 90220174 A 19900823
IPC: * A63F-001/00
Language of Document: Japanese
Patent (No,Kind,Date): JP 2795449 B2 19980910
Patent Assignee: ADOMINISUTOREETAAZU OBU ZA TSU
Author (Inventor): KOI DEEBITSUDO ETSUCHI; MOROO JATSUKUUPIEERU
Priority (No,Kind,Date): US 100571 A 19870924
Applic (No,Kind,Date): JP 88509311 A 19880923
IPC: * C07K-014/46; A61K-038/22; C07K-014/575
Language of Document: Japanese
Patent (No,Kind,Date): JP 2919889 B2 19990719
Patent Assignee: ADOMINISUTOREETAAZU OBU ZA TSU
Author (Inventor): KOI DEIBITSUDO EICHI; MOROO JATSUKUPIEERU; TEIRAA JON II; KIMU SUN HYUKU
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): JP 89511442 A 19891013
IPC: * C07K-014/575; C07K-007/06; A61K-031/00; A61K-038/00; A61K-038/04; A61K-038/22
Language of Document: Japanese
Patent (No,Kind,Date): JP 2502016 T2 19900705
Priority (No,Kind,Date): WO 88US3286 W 19880923; US 100571 A 19870924
Applic (No,Kind,Date): JP 88509311 A 19880923
IPC: * C07K-007/06; A61K-037/24; C07K-001/04; C07K-007/08; C07K-099-00
CA Abstract No: * 111(11)097733N
Derwent WPI Acc No: * C 89-095447
Language of Document: Japanese
Patent (No,Kind,Date): JP 4502922 T2 19920528
Priority (No,Kind,Date): WO 90US4633 W 19900816; US 394727 A 19890816
Applic (No,Kind,Date): JP 90511667 A 19900816

IPC: * C07K-007/06; A61K-037/02; C07K-099-00
CA Abstract No: * 115(15)151906U
Derwent WPI Acc No: * C 91-087240
Language of Document: Japanese
Patent (No,Kind,Date): JP 4504406 T2 19920806
Priority (No,Kind,Date): WO 89US4616 W 19891013; US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): JP 89511442 A 19891013
IPC: * C07K-007/06; A61K-037/02; A61K-037/24; A61K-037/43; C07K-099-00
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241
Language of Document: Japanese
Patent (No,Kind,Date): JP 4506664 T2 19921119
Priority (No,Kind,Date): WO 90US4646 W 19900817; US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): JP 90512265 A 19900817
IPC: * C07K-007/06; C05B
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: Japanese

MONACO (MC)
Patent (No,Kind,Date): MC 2144 A 19920219
PEPTIDES THERAPEUTIQUES (French)
Patent Assignee: UNIV TULANE
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; TAYLOR JOHN E; KIM SUN HYUK
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; WO 89US4616 W 19891013; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): MC 2144 A 19891013
IPC: * C07K
CA Abstract No: * 112(17)158978R; 113(19)172755T; 115(15)150377K; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-309505; C 90-147822; C 91-087241; C 95-169633; C 98-229235; C 98-296827; C 99-189718
Language of Document: French
Patent (No,Kind,Date): MC 2193 A 19921005
ENSEMBLE DE JEU COMPORTANT DES PIECES DE JEU A DEUX FACES (French)
Patent Assignee: STEWART MILTON LAMLE
Author (Inventor): STEWART MILTON LAMLE
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): MC 2144 A 19900820
IPC: * A63F
Derwent WPI Acc No: * G 91-059703
Language of Document: French

NORWAY (NO)
Patent (No,Kind,Date): NO 8902060 A 19890721
TERAPEUTISKE PEPTIDER. (Norwegian)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 W 19880923
Applic (No,Kind,Date): NO 892060 A 19890523
IPC: * C07K-007/02; C07K-007/00
CA Abstract No: * 111(11)097733N; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-095447; C 95-169633; C 98-229235; C 98-296827; C 99-189718
Language of Document: Norwegian
Patent (No,Kind,Date): NO 9003697 A 19910225
SPILLSETT MED TOSIDEDE SPILLBRIKKER. (Norwegian)
Patent Assignee: LAMLE STEWART M
Author (Inventor): LAMLE STEWART MILTON
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): NO 903697 A 19900822

IPC: * A63F-009/00
Derwent WPI Acc No: * G 91-059703
Language of Document: Norwegian

Patent (No,Kind,Date): NO 9200678 A 19920406
TERAPEUTISKE PEPTIDER (Norwegian)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; KIM SUN HYUK
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330; WO 90US4646 W 19900817
Applic (No,Kind,Date): NO 92678 A 19920220
IPC: * C07K-005/02; C07K-007/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/06; C07K-007/08; C07K-007/10
CA Abstract No: * 113(19)172755T; 115(15)150377K; 128(18)213739W
Derwent WPI Acc No: * C 90-147822; C 91-087241; C 98-229235; C 99-189718
Language of Document: Norwegian

Patent (No,Kind,Date): NO 8902060 A0 19890523
TERAPEUTISKE PEPTIDER. (Norwegian)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 W 19880923
Applic (No,Kind,Date): NO 892060 A 19890523
IPC: * C07K
Derwent WPI Acc No: * C 89-095447
Language of Document: Norwegian

Patent (No,Kind,Date): NO 9003697 A0 19900822
SPILLSETT MED TOSIDEDE SPILLBRIKKER. (Norwegian)
Patent Assignee: LAMLE STEWART MILTON (US)
Author (Inventor): LAMLE STEWART MILTON
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): NO 903697 A 19900822
IPC: * A63F
Language of Document: Norwegian

Patent (No,Kind,Date): NO 9200678 A0 19920220
TERAPEUTISKE PEPTIDER (Norwegian)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H; MOREAU JACQUES-PIERRE; KIM SUN HYUK
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330; WO 90US4646 W 19900817
Applic (No,Kind,Date): NO 92678 A 19920220
IPC: * C07K-005/02
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: Norwegian

Patent (No,Kind,Date): NO 178306 B 19951120
ANALOGIFREMGANGSMAATE VED FREMSTILLING AV BOMBESIN-ANTAGONISTPEPTID (Norwegian)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 W 19880923
Applic (No,Kind,Date): NO 892060 A 19890523
IPC: * C07K-007/06; C07K-007/08
CA Abstract No: * 111(11)097733N; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-095447; C 95-169633; C 98-229235; C 98-296827; C 99-189718
Language of Document: Norwegian

Patent (No,Kind,Date): NO 302619 B1 19980330
ANALOGIFREMGANGSMAATE FOR FREMSTILLING AV ET TERAPEUTISK PEPTID (Norwegian)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330; WO 90US4646 W 19900817
Applic (No,Kind,Date): NO 92678 A 19920220

IPC: * C07K-005/02
CA Abstract No: * 113(19)172755T; 115(15)150377K; 128(18)213739W
Derwent WPI Acc No: * C 90-147822; C 91-087241; C 98-229235; C 99-189718
Language of Document: Norwegian
Patent (No,Kind,Date): NO 178306 C 19960228
ANALOGIFREMGANGSMAATE VED FREMSTILLING AV BOMBESIN-ANTAGONISTPEPTID (Norwegian)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 100571 A 19870924; WO 88US3286 W 19880923
Applic (No,Kind,Date): NO 892060 A 19890523
IPC: * C07K-007/06; C07K-007/08
CA Abstract No: * 111(11)097733N; 123(21)286737A
Derwent WPI Acc No: * C 89-095447; C 95-169633
Language of Document: Norwegian

NEW ZEALAND (NZ)
Patent (No,Kind,Date): NZ 234993 A 19920428
STACKABLE INDICIA BEARING PIECES AS GAME SET (English)
Patent Assignee: LAMLE STEWART M
Author (Inventor): LAMLE STEWART MILTON
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): NZ 234993 A 19900821
IPC: * A63F-001/02; A63F-009/20
Derwent WPI Acc No: * G 91-059703
Language of Document: English

PORTUGAL (PT)
Patent (No,Kind,Date): PT 95016 A 19910418
PROCESSO PARA A PREPARACAO DE PEPTIDOS TERAPEUTICOS (English; French; German; Portugese)
Patent Assignee: UNIV TULANE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): PT 95016 A 19900816
IPC: * C07K-001/00
Derwent WPI Acc No: * C 91-087240
Language of Document: Portugese
Patent (No,Kind,Date): PT 95057 A 19910522
PROCESSO PARA A PREPARACAO DE PEPTIDOS TERAPEUTICOS (English; French; German; Portugese)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID HOWARD (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 397169 A 19890821
Applic (No,Kind,Date): PT 95057 A 19900821
IPC: * C07K-007/08; A61K-037/02
CA Abstract No: * 113(19)172755T
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: Portugese
Patent (No,Kind,Date): PT 95016 B 19970528
PROCESSO PARA A PREPARACAO DE PEPTIDOS TERAPEUTICOS (English; French; German; Portugese)
Patent Assignee: UNIV TULANE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): PT 95016 A 19900816
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Portugese
Patent (No,Kind,Date): PT 95057 B 19971231
PROCESSO PARA A PREPARACAO DE PEPTIDOS TERAPEUTICOS (English; French; German; Portugese)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID HOWARD (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 397169 A 19890821

Applic (No,Kind,Date): PT 95057 A 19900821
IPC: * C07K-007/02; C07K-007/06; C07K-007/08; C07K-014/595
CA Abstract No: * 113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 90-147822; C 91-087241
Language of Document: Portugese

RUSSIA (RU)
Patent (No,Kind,Date): RU 2088592 C1 19970827
THERAPEUTIC PEPTIDES OR THEIR PHARMACEUTICALLY ACCEPTABLE SALTS (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): WO 89US4616 W 19891013; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): RU 4895537 A 19891013
IPC: * C07K-007/06; A61K-038/08
CA Abstract No: * 113(19)172755T; 115(15)150377K; 123(21)286737A
Derwent WPI Acc No: * C 90-147822; C 91-087241; C 95-169633
Language of Document: Russian

SLOVAKIA (SK)
Patent (No,Kind,Date): SK 9004028 A3 20000711
SUBSTANCE P ANALOG (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): SK 904028 A 19900816
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Slovak
Patent (No,Kind,Date): SK 280796 B6 20000711
SUBSTANCE P ANALOG (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816
Applic (No,Kind,Date): SK 904028 A 19900816
IPC: * C07K-007/02; C07K-007/22; A61K-038/08
CA Abstract No: * 115(15)151906U; 123(21)286737A
Derwent WPI Acc No: * C 91-087240; C 95-169633
Language of Document: Slovak

UNITED STATES OF AMERICA (US)
Patent (No,Kind,Date): US 4998737 A 19910312
TWO-SIDED PLAYING PIECE GAME SET (English)
Patent Assignee: LAMLE STEWART M (US)
Author (Inventor): LAMLE STEWART M (US)
Priority (No,Kind,Date): US 398172 A 19890823
Applic (No,Kind,Date): US 398172 A 19890823
National Class: * 273296000; 273292000
IPC: * A63F-001/00
Language of Document: English
Patent (No,Kind,Date): US 5084555 A 19920128
AN OCTAPEPTIDE BOMBESIN ANALOG (English)
Patent Assignee: UNIV TULANE (US); BIOMEASURE INC (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN H (US)
Priority (No,Kind,Date): US 397169 B2 19890821; US 376555 B2 19890707; US 317941 B2 19890302; US 282328 A2 19881209; US 257998 B2 19881014; US 248771 B2 19880923; US 207759 B2 19880616; US 204171 B2 19880608; US 173311 B2 19880325; US 100571 B2 19870924
Applic (No,Kind,Date): US 502438 A 19900330
National Class: * 530328000; 530309000; 530323000; 530324000; 530325000; 530326000; 530327000; 530329000; 530332000
IPC: * C07K-007/06; C07K-007/30
CA Abstract No: * 111(11)097733N; 112(17)158978R; 112(19)179890W;

113(19)172755T; 115(15)150377K
Derwent WPI Acc No: * C 89-095447; C 89-280003; C 89-309505; C 90-147822; C 91-087241
Language of Document: English

Patent (No,Kind,Date): US 5162497 A 19921110
BRADYKININ ANALOGS WITH NON-PEPTIDE BOND (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN H (US)
Priority (No,Kind,Date): US 257998 B2 19881014; US 248771 B2 19880923; US 207759 B2 19880616; US 204171 B2 19880608; US 173311 B2 19880325; US 100571 B2 19870924
Applic (No,Kind,Date): US 282328 A 19881209
National Class: * 530314000; 530332000; 530328000; 514803000; 930030000; 930DIG790; 930DIG600; 930DIG601
IPC: * C07K-007/00; C07K-007/18
CA Abstract No: * 111(11)097733N; 112(17)158978R; 112(19)179890W; 113(19)172755T
Derwent WPI Acc No: * C 89-095447; C 89-280003; C 89-309505; C 90-147822
Language of Document: English

Patent (No,Kind,Date): US 5410019 A 19950425
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 860675 A 19920330; US 394727 B2 19890816; US 317941 B2 19890302; US 282328 A2 19881209; US 257998 B2 19881014; US 248771 B2 19880923; US 207759 B2 19880616; US 204171 B2 19880608; US 173311 B2 19880325; US 100571 B2 19870924
Applic (No,Kind,Date): US 860675 A 19920330
Addnl Info: 5162497 Patented
National Class: * 530323000; 530327000; 530328000; 530329000; 530330000
IPC: * C07K-007/02; C07K-007/06
CA Abstract No: * 111(11)097733N; 112(17)158978R; 112(19)179890W; 113(19)172755T; 115(15)151906U; 123(21)286737A; 128(18)213739W; 129(02)016394Z; 123(21)286737A
Derwent WPI Acc No: * C 89-095447; C 89-280003; C 89-309505; C 90-147822; C 91-087240; C 95-169633; C 98-229235; C 98-296827; C 99-189718; C 95-169633
Language of Document: English

Patent (No,Kind,Date): US 5723578 A 19980303
Peptide analogs of bombesin (English)
Patent Assignee: ADMINISTRATORS OF TULANE EDUCA (US); BIOMEASURE INC (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 488099 A 19950607; US 337127 A2 19941110; US 779039 B2 19911018; US 502438 A2 19900330; US 397169 B2 19890821; US 376555 B2 19890707; US 317941 B2 19890302; US 282328 A2 19881209; US 257998 B2 19881014; US 248771 B2 19880923; US 207759 B2 19880616; US 204171 B2 19880608; US 173311 B2 19880325; US 100571 B2 19870924
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National Class: * 530326000; 530327000; 530328000
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Derwent WPI Acc No: ; C 98-229235
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Patent (No,Kind,Date): US 5750646 A 19980512
BRADYKININ ANALOGS WITH NON-PEPTIDE BOND (English)
Patent Assignee: UNIV TULANE (US); BIOMEASURE INC (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 408197 A 19950322; US 880179 B2 19920507; US 282328 A2 19881209; US 257998 B2 19881014; US 248771 B2 19880923; US 207759 B2 19880616; US 204171 B2 19880608; US

173311 B2 19880325; US 100571 A2 19870924
Applic (No,Kind,Date): US 408197 A 19950322
Addnl Info: 5162497 Patented
National Class: * 530314000; 530328000; 530332000
IPC: * A61K-038/00; C07K-005/00; C07K-007/00; C07K-017/00
CA Abstract No: * 111(11)097733N; 112(17)158978R; 112(19)179890W; 113(19)172755T; 123(21)286737A; 128(18)213739W; 129(02)016394Z; 129(02)016394Z
Derwent WPI Acc No: * C 89-095447; C 89-280003; C 89-309505; C 90-147822; C 95-169633; C 98-229235; C 98-296827; C 99-189718; C 98-296827
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Patent (No,Kind,Date): US 5877277 A 19990302
OCTAPEPTIDE BOMBESIN ANALOGS (English)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 337127 A 19941110; US 779039 B1 19911018; US 502438 A2 19900330; US 397169 B2 19890821; US 376555 B2 19890707; US 317941 B2 19890302; US 282328 A2 19881209; US 257998 B2 19881014; US 248771 B2 19880923; US 207759 B2 19880616; US 204171 B2 19880608; US 173311 B2 19880325; US 100571 B2 19870924
Applic (No,Kind,Date): US 337127 A 19941110
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National Class: * 530328000; 530323000
IPC: * C07K-005/00; C07K-007/00; C07K-007/06; A61K-038/00
CA Abstract No: * 111(11)097733N; 112(17)158978R; 112(19)179890W; 113(19)172755T; 115(15)150377K; 123(21)286737A; 128(18)213739W; 129(02)016394Z
Derwent WPI Acc No: * C 89-095447; C 89-280003; C 89-309505; C 90-147822; C 91-087241; C 95-169633; C 96-455920; C 98-229235; C 98-296827; C 99-189718; C 99-189718
Language of Document: English

Patent (No,Kind,Date): US 20030050436 AA 20030313
Octapeptide bombesin analogs (English)
Patent Assignee: BIOMEASURE INC MASSACHUSETTS C (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 4530 A 20011023; US 260846 A3 19990302; US 337127 A3 19941110; US 779039 B1 19911018; US 502438 A2 19900330; US 397169 B2 19890821; US 376555 B2 19890707; US 317941 B2 19890302; US 282328 A2 19881209; US 257998 B2 19881014; US 248771 B2 19880923; US 207759 B2 19880616; US 204171 B2 19880608; US 173311 B2 19880325; US 100571 B2 19870924
Applic (No,Kind,Date): US 4530 A 20011023
Addnl Info: 6307017 Patented; 5877277 Patented; 5084555 Patented; 5162497 Patented
National Class: * 530328000; 530329000
IPC: * C07K-007/08; C07K-007/06
Derwent WPI Acc No: ; C 03-810756
Language of Document: English

Patent (No,Kind,Date): US 6307017 BA 20011023
Octapeptide bombesin analogs (English)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 260846 A 19990302; US 337127 A3 19941110; US 779039 B2 19911018; US 502438 A2 19900330; US 397169 B2 19890821; US 376555 B2 19890707; US 317941 B2 19890302; US 282328 A2 19881209; US 257998 B2 19881014; US 248771 B2 19880923; US 207759 B2 19880616; US 204171 B2 19880608; US 173311 B2 19880325; US 100571 B2 19870924
Applic (No,Kind,Date): US 260846 A 19990302
Addnl Info: 5877277 Patented; 5084555 Patented; 5162497 Patented
National Class: * 530328000; 530300000; 530323000; 514012000; 514015000
IPC: * A61K-038/00; A61K-038/04; C07K-005/00; C07K-007/00

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WORLD INTELLECTUAL PROPERTY ORGANIZATION, PCT (WO)
Patent (No,Kind,Date): WO 8902897 A1 19890406
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE (US); COY DAVID HOWARD (US); MOREAU JACQUES PIERRE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
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THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US)
Priority (No,Kind,Date): US 173311 A 19880325
Applic (No,Kind,Date): WO 89US1216 A 19890322
Designated States: (National) AU; DK; FI; JP; NO
Filing Details: WO 13000 With international search report; Before expiration of time limit for amending the claims and to be republished in the event of the receipt of the amendments
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Patent (No,Kind,Date): WO 8909231 A1 19891005
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 173311 A 19880325; US 282328 A 19881209
Applic (No,Kind,Date): WO 89US1259 A 19890327
Designated States: (National) AU; DK; FI; JP; NO (Regional) AT; BE; CH; DE; FR; GB; IT; LU; NL; SE
Filing Details: WO 10000 With international search report
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CA Abstract No: ; 112(17)158978R
Derwent WPI Acc No: ; C 89-309505
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Patent (No,Kind,Date): WO 9003980 A1 19900419
THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); TAYLOR JOHN E (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 257998 A 19881014; US 282328 A 19881209; US 317941 A 19890302; US 376555 A 19890707; US 397169 A 19890821
Applic (No,Kind,Date): WO 89US4616 A 19891013
Designated States: (National) AU; BB; BG; BR; DK; FI; HU; JP; KP; KR; LK; MC; MG; MW; NO; RO; SD; SU (Regional) AT; BE; BF; BJ; CF; CG; CH; CM; DE; FR; GA; GB; IT; LU; ML; MR; NL; SE; SN; TD; TG
Filing Details: WO 10000 With international search report
IPC: * C07K-007/02; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: ; 113(19)172755T
Derwent WPI Acc No: ; C 90-147822
Language of Document: English

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THERAPEUTIC PEPTIDES (English)
Patent Assignee: UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US)
Priority (No,Kind,Date): US 394727 A 19890816

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Filing Details: WO 130000 With international search report; Before expiration of time limit for amending the claims and to be republished in the event of the receipt of the amendments
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02; C07K-007/06; C07K-007/08
CA Abstract No: ; 115(15)151906U
Derwent WPI Acc No: ; C 91-087240
Language of Document: English

Patent (No,Kind,Date): WO 9102746 A1 19910307
THERAPEUTIC PEPTIDES (English)
Patent Assignee: BIOMEASURE INC (US); UNIV TULANE (US)
Author (Inventor): COY DAVID H (US); MOREAU JACQUES-PIERRE (US); KIM SUN HYUK (US)
Priority (No,Kind,Date): US 397169 A 19890821; US 502438 A 19900330
Applic (No,Kind,Date): WO 90US4646 A 19900817
Designated States: (National) AU; CA; FI; JP; NO (Regional) AT; BE; CH; DE; DK; ES; FR; GB; IT; LU; NL; SE
Filing Details: WO 130000 With international search report; Before expiration of time limit for amending the claims and to be republished in the event of the receipt of the amendments
IPC: * C07K-005/02; C07K-005/06; C07K-005/08; C07K-005/10; C07K-007/02; C07K-007/06; C07K-007/08; C07K-007/10; C07K-007/30
CA Abstract No: ; 115(15)150377K
Derwent WPI Acc No: ; C 91-087241
Language of Document: English

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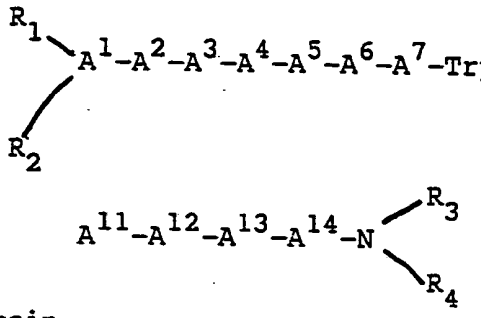
the non-peptide bond, failing to exhibit the in vivo activity of naturally occurring bombesin. (A detailed discussion of the chemistry of non-peptide bonds is given in Coy et al. (1988) Tetrahedron 44,3:835-841, hereby incorporated by reference.)

Preferably, naturally occurring bombesin is characterized in that one or more amino acids in the amino terminal half of bombesin are hydrogen bonded to one or more amino acids in the carboxy terminal half of bombesin, and the non-peptide bond of the linear peptide decreases that hydrogen bonding, thereby destroying biological activity. It is believed that many of the linear peptides of the invention are analogs of bombesin whose biological activity depends at least in part on their ability to form tertiary "hairpin" configurations in which amino acids in the amino terminal ("left") half of the molecule are hydrogen bonded to amino acids in the carboxy terminal ("right") half of the molecule, and that the pseudopeptide bond introduced according to the invention interferes with this hydrogen bonding, hindering the formation of the hairpin configuration on which activity depends. One may expect the loss of the ability to hydrogen bond to affect the biological activity of the molecule either by the loss of structural stability conferred by the transannular bonding or by the inability of the backbone to hydrogen bond to the receptor. Additionally, the increased flexibility of the molecule about the reduced bond compared with the rigidity of the normal peptide amide bond is expected to alter the conformational integrity of the molecule and thus its biological activity.

It is apparent from the above that the linear peptides for which introduction of a pseudopeptide bond is useful in creating or enhancing antagonist activity are those in which activity is associated with a site within the amino acid chain (some peptides, e.g., CCK, have their active sites at an end of the peptide). The pseudopeptide bond can be introduced in a

region involved in receptor binding, or in a non-binding region; it has been shown (Nagain et al., Peptides, 8:1023-28 (1987)) that a pseudopeptide bond introduced in the binding region does not prevent binding. Generally, useful classes of peptides in which this modification can be made are those in which at least one amino acid involved in the active site is located in the carboxy terminal half of the molecule; the non-peptide bond is introduced between this amino acid and one adjacent to it.

One class of peptides of the invention is an effective bombesin antagonist peptide of formula (1):



wherein

A^1 = pGlu or is deleted;

A^2 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, ß-naphthylalanine or is deleted;

A^3 = Arg, D-Arg, Lys, D-Lys or is deleted;

A^4 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, ß-naphthylalanine or is deleted;

A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, D-Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, ß-naphthylalanine, D-Ala or is deleted;

A^6 = Gln, Asn, Gly, Ala, D-Ala, N-Ac-D-Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe(X = F, Cl, Br, OH or CH_3), Trp, p-Glu, ß-naphthylalanine or is deleted;

A^7 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, D-Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, His, or ß-naphthylalanine;

A^8 = Trp;

A^9 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, or ß-naphthylalanine;

A^{10} = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, or ß-naphthylalanine;

A^{11} = Gly, or D-Ala;

A^{12} = His, Phe, or p-X-Phe (X = F, Cl, Br, OH, CH_3);

A^{13} = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, ß-naphthylalanine;

A^{14} = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, or ß-naphthylalanine;

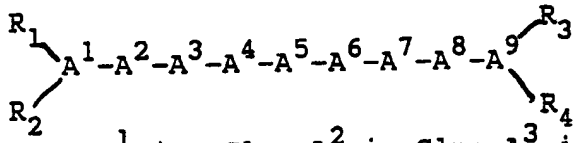
provided that

each R_1, R_2, R_3 and R_4, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, COE_1 (where E_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or $COOE_2$ (where E_2 is C_{1-10} alkyl or C_{7-10} phenylalkyl), and R_1 and R_2 are bonded to the N-terminal amino

acid of said peptide, which can be A^1, A^2, A^3, A^4, A^5, A^6, or A^7, provided that when one of R_1 or R_2 is COE_1 or $COOE_2$, the other must be H, and when one of R_3 or R_4 is COE_1 or $COOE_2$, the other must be H, and further provided that when A^1 = pGlu, R_1 must be H and R_2 must be the portion of Glu that forms the imine ring in pGlu; and for each of the residues A^7, A^8, A^9, A^{10}, A^{11}, A^{12}, and A^{13}, independently, the carbon atom participating in the amide bond between that residue and the nitrogen atom of the alpha amino group of the adjacent amino acid residue may be a carbonyl carbon or may be reduced to a methylene carbon, provided that at least one such carbon atom must be reduced to a methylene carbon (i.e., at least one of the subject peptide CONH bonds must be replaced by a non-peptide, i.e., pseudopeptide, CH_2NH bond); or a pharmaceutically acceptable salt thereof. (Where no D- or L-isomeric designation is given herein, the naturally occurring L-isomer is intended.)

Preferably, an effective bombesin antagonist peptide has, for each of the residues A^{11}, A^{12}, and A^{13}, independently, the carbon atom participating in the amide bond between that residue and the nitrogen atom of the alpha amino group of the adjacent amino acid residue which may be a carbonyl carbon or may be reduced to a methylene carbon, provided that at least one such carbon atom must be reduced to a methylene carbon; or a pharmaceutically acceptable salt thereof. Most preferably, the bombesin antagonist peptide has A^1 through A^6 deleted and the carbon atom participating in the amide bond between Leu^{13} and Leu^{14} is a methylene carbon, or a pharmaceutically acceptable salt thereof

Another class of peptides of the invention are bombesin-related antagonist peptides derived from litorin and of the amino acid formula:



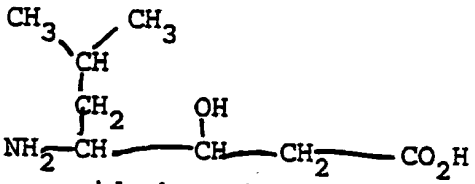
wherein A^1 is pGlu; A^2 is Gln; A^3 is Trp; A^4 is Ala; A^5 is Val; A^6 is Gly or D-Ala; A^7 is His; A^8 is Phe or Leu; and A^9 is Met or Leu; provided that the carbon atom participating in the amide bond between the A^8 residue and the nitrogen atom of the alpha amino group of the adjacent amino acid residue may be a carbonyl carbon or may be reduced to a methylene carbon, or a pharmaceutically acceptable salt thereof.

Peptides of the invention that contain a pseudopeptide bond substitution within the active site of the naturally occurring peptide are antagonists to the biological activity of the naturally occurring bombesin peptide, with one exception which we have observed; the linear analog of bombesin BIM-26027 [$Val^{10}\psi[CH_2NH]Leu^{14}$]BN is an agonist of the biological activity of naturally occurring bombesin. (Non-peptide bonds are symbolized herein by "$\psi[CH_2NH]$" or "ψ".) Therefore, a third class of peptides of the invention are effective bombesin agonists of the formula (1) recited above, including, for each of the residues A^9, A^{10}, A^{11}, A^{12}, A^{13}, and A^{14}, independently, the carbon atom participating in the amide bond between that residue and the nitrogen atom of the alpha amino group of the adjacent amino acid residue may be a carbonyl carbon or may be a non-peptide bond, provided that the non-peptide bond may be a carbonyl carbon having been reduced to a methylene carbon; further provided that at least one

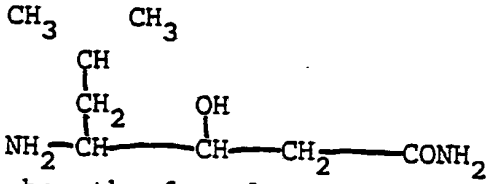
such carbon atom must be reduced to a methylene carbon; or a pharmaceutically acceptable salt thereof. Most preferred is the bombesin agonist having the formula pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Leu[$Val^{10}\Psi[CH_2NH]Leu^{14}$].

Other agonist analogues are peptides in which either the pseudopeptide bond is not located in the active site of the naturally occurring peptide, or in which two amino acid residues of the active site are replaced by statine or AHPPA.

(Statine has the chemical structure



and statine-amide has the structure



and AHPPA has the formula:

(3S,4S)-4-amino-3-hydroxy-5-phenylpentanoic acid.)

Therefore, a fourth class of peptides of the invention is an effective bombesin agonist which is an analog of naturally occurring, biologically active bombesin having an active site, which includes positions A^9, A^{10}, A^{11}, A^{12}, A^{13}, and A^{14}, and a binding site responsible for the binding of bombesin to a receptor on a target cell, the analog having either (a) a non-peptide bond outside of the active site of bombesin, or (b) having at least one statine or AHPPA residue in place of two naturally occurring amino acids of the active site; and further, the peptide can contain statine or AHPPA when all bonds between amino acid

residues are peptide bonds and, further, when an amino acid residue is statine or AHPPA, the amino acid to the right of it in the formula is deleted, so that the analog is capable of binding to the receptor and, by virtue of the statine or AHPPA residue, exhibiting enhanced in vivo biological activity compared to naturally occurring bombesin. Most preferred in this class is the bombesin agonist having the amino acid formula pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-[Sta^{13},Des Met^{14}].

The bombesin antagonists and agonists of the invention are suitable for the treatment of all forms of cancer where bombesin-related substances act as autocrine or paracrine mitotic factors, especially pancreas and small-cell lung carcinoma.

In formula (1), when R_1, R_2, R_3 or R_4 is an aromatic, lipophilic group, the in vivo activity can be long lasting, and delivery of the compounds of the invention to the target tissue (e.g., the lungs) can be facilitated.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description of the Preferred Embodiments

We will first briefly describe the table.

Table

Table I shows formulas for the pseudo-peptide analogues and results of in vitro inhibition of [^{125}I]GRP binding to cerebral cortical and 3T3 bombesin receptors, and bombesin-stimulated [^{3}H]Thymidine uptake by cultured 3T3 cells.

We now describe the structure, synthesis, and use of the preferred embodiments of the invention.

Structure

The peptides of the invention all have a non-peptide bond in at least one of the indicated position, except for the statine or AHPPA substituted analogs, such as sta^{13}-des Met^{14} bombesin. By non-peptide bond is meant that the carbon atom participating in the bond between two residues is reduced from a carbonyl carbon to a methylene carbon. The peptide bond reduction method which yields this non-peptide bond is described in Coy et al., U.S. patent application, Serial No. 879,348, assigned to the same assignee as the present application, hereby incorporated by reference. Any one or all of the amino acids in positions 1 through 6 of the bombesin antagonists may be deleted from the peptides, and the peptides are still active as antagonists or agonists.

The peptides of the invention can be provided in the form of pharmaceutically acceptable salts. Examples of preferred salts are those with therapeutically acceptable organic acids, e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, salicylic, methanesulfonic, toluenesulfonic, or pamoic acid, as well as polymeric acids such as tannic acid or carboxymethyl cellulose, and salts with inorganic acids such as the hydrohalic acids, e.g., hydrochloric acid, sulfuric acid, or phosphoric acid.

Synthesis of Bombesin Antagonists

The synthesis of the bombesin antagonist pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leuψ[CH_2-NH]Leu-NH_2 follows. Other bombesin antagonists and agonists can be prepared by making appropriate modifications of the following synthetic method.

The first step is the preparation of the intermediate pGlu-Gln-Arg(tosyl)-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His(benzyloxycarbonyl)-Leuψ[CH_2NH]Leu-benzhydrylamine resin, as follows.

Benzhydrylamine-polystyrene resin (Vega Biochemicals, Inc.) (0.97 g, 0.5 mmole) in the chloride ion form is placed in the reaction vessel of a Beckman 990B peptide synthesizer programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid (TFA) in methylene chloride (2 times for 1 and 25 min. each); (c) methylene chloride; (d) ethanol; (e) methylene chloride; and (f) 10% triethylamine in chloroform.

The neutralized resin is stirred with alpha-t-butoxycarbonyl(Boc)-leucine and diisopropylcarbodiimide (1.5 mmole each) in methylene chloride for 1 hour, and the resulting amino acid resin is then cycled through steps (a) to (f) in the above wash program. Boc-leucine aldehyde (1.25 mmoles), prepared by the method of Fehrentz and Castro, Synthesis, p. 676 (1983), is dissolved in 5 ml of dry dimethylformamide (DMF) and added to the resin TFA salt suspension followed by the addition of 100 mg (2 mmoles) of sodium cyanoborohydride (Sasaki and Coy, Peptides 8:119-121 (1987); Coy et al., id.). After stirring for 1 hour, the resin mixture is found to be negative to ninhydrin reaction (1 min.), indicating complete derivatization of the free amino group.

The following amino acids (1.5 mmole) are then coupled successively in the presence diisopropylcarbodiimide (1.5 mmole), and the resulting amino acid resin is cycled through washing/deblocking steps (a) to (f) in the same procedure as above: Boc-His(benzyloxycarbonyl), Boc-Gly, Boc-Val, Boc-Ala,

Boc-Trp, Boc-Gln (coupled in the presence of equivalent of hydroxybenzotriazole), Boc-Asn (coupled in the presence of 1 equivalent of hydroxybenzotriazole), Boc-Gly (coupled as a 6 M excess of the p-nitrophenyl ester), Boc-Leu, Boc-Arg(tosyl), Boc-Gln (coupled as a 6 M excess of the p-nitrophenylester), and pGlu. The completed resin is then washed with methanol and air dried.

The resin described above (1.6 g, 0.5 mmole) is mixed with anisole (5 ml) and anhydrous hydrogen fluoride (35 ml) at 0°C and stirred for 45 min. Excess hydrogen fluoride is evaporated rapidly under a stream of dry nitrogen, and free peptide is precipitated and washed with ether. The crude peptide is dissolved in a minimum volume of 2 M acetic acid and eluted on a column (2.5 x 100 mm) of Sephadex G-25 (Pharmacia Fine Chemicals, Inc.). Fractions containing a major component by uv absorption and thin layer chromatography (TLC) are then pooled, evaporated to a small volume and applied to a column (2.5 x 50 cm) of octadecylsilane-silica (Whatman LRP-1, 15-20 μm mesh size).

The peptide is eluted with a linear gradient of 0-30% acetonitrile in 0.1% trifluoroacetic acid in water. Fractions are examined by TLC and analytical high performance liquid chromatography (HPLC) and pooled to give maximum purity. Repeated lyophilization of the solution from water gives 60 mg of the product as a white, fluffy powder.

The product is found to be homogeneous by HPLC and TLC. Amino acid analysis of an acid hydrolysate confirms the composition of the peptide. The presence of the Leuψ[CH_2-NH]Leu bond is demonstrated by fast atom bombardment mass spectrometry.

pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Alaψ[CH_2-NH]Val-Gly-His-Leu-Met-NH_2 and pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leuψ[CH_2NH]Met-NH_2 are prepared in similar yields in an analogous fashion by appropriately modifying the above procedure.

A statine or AHPPA residue can be substituted in place of any two amino acids of the peptide, where the peptide contains no pseudopeptide bonds. For example, sta^{13}-des Met^{14} bombesin was prepared in an analagous fashion by first coupling statine to the resin and then proceeding with the addition of Boc-His(benzylocarbonyl). Statine or Boc-statine can be synthesized according to the method of Rich et al., 1978, J. Organic Chem. 43; 3624; and Rich et al., 1980, J. Med. Chem. 23: 27, and AHPPA can be synthesized according to the method of Hui et al., 1987, J. Med. Chem. 30: 1287.

Synthesis of Sta^{13}-Des-Met^{14} Bombesin

Solid-phase synthesis of the peptide pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Sta-NH_2 was accomplished through the use of the following procedures in which alpha-t-butoxycarbonyl statine (prepared by the procedure of Rich et al., J. Org. Chem. 1978, 43, 3624) is first coupled to methylbenzhydrylamine-polystyrene resin. After acetylation, the intermediate p-Glu-Gln-Arg(tosyl)-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His(benzyloxycarbonyl)-Sta-methylbenzhydrylamine resin is prepared. The synthetic procedure used for this preparation follows in detail:

1. Incorporation of alpha-t-butoxycarbonyl statine on methylbenzhydrylamine resin.

Methylbenzhydrylamine-polystyrene resin (Vega Biochemicals, Inc.) (1.0 g, 0.73 mmol) in the chloride ion form is placed in the reaction vessel of a Vega 250C Coupler peptide synthesizer. The synthesizer was programmed to perform the following reactions: (a) methylene chloride; (b) 10% triethylamine in chloroform; (c) methylene chloride; and (d) dimethylformamide.

The neutralized resin is mixed for 18 hours with the preformed active ester made from alpha-t-butoxycarbonyl statine (1.46 mmol), diisopropyl carbodiimide (2 mmol), and hydroxybenzotriazole hydrate (1.46 mmol in dimethylformamide at 0° C. for one hour. The resulting amino acid resin is washed on the synthesizer with dimethylformamide and then methylene chloride. The resin mixture at this point was found by the Kaiser ninhydrin test (5 minutes) to have an 84% level of statine incorporation on the resin.

Acetylation was performed by mixing the amino-acid resin for 15 minutes with N-acetyl imidazole (5 mmol) in methylene chloride. Derivitization to the 94-99% level of the free amino groups of the resin was indicated by the Kaiser ninhydrin test (5 minutes). The Boc-statine-resin is then washed with methylene chloride.

2. Couplings of the Remaining Amino Acids.

The peptide synthesizer is programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluroacetic acid (TFA) in methylene chloride (2 times for 5 and 25 min. each); (c) methylene chloride; (d) isopropyl alcohol; (e) 10% triethylamine in chloroform; and (f) methylene chloride.

The following amino acids (2.19 mmol) are then coupled successively by diisopropyl carbodiimide (4

mmol) alone or diisopropyl carbodiimide (4 mmol) plus hydroxybenzotriazole hydrate (1.47 or 0.73 mmol) and the resulting peptide-resin is washed on the synthesizer with dimethylformamide and then methylene chloride, and then cycled through the washing and deblocking steps (a) to (f) in the procedure described above.

Boc-His (benzyloxycarbonyl) (coupled in the presence of 2 equivalents hydroxybenzotriazole); Boc-Gly; Boc-Val; Boc-Ala; Boc-Trp; Boc-Gln and Boc Asn (coupled as the preformed hydroxybenzotriazole active esters made by reaction at 0° C. for one hour with 1 equivalent hydroxybenzotriazole hydrate); Boc-Gly; Boc-Leu; Boc-Arg(tosyl), Boc-Gln, and pGlu (also coupled as the preformed active esters of hydroxybenzotriazole made by reaction at 0° C. for one hour with 1 equivalent hydroxybenzotriazole hydrate). The completed peptide-resin is then washed with methanol and air dried.

The peptide-resin described above (1.60 g, 0.73 mmol) is mixed with anisole (2.5 mL), dithiothreitol (50 mg), and anhydrous hydrogen fluoride (30 mL) at 0° C. for one hour. Excess hydrogen fluoride is evaporated rapidly under a stream of dry nitrogen, and the free peptide is precipitated and washed with ether. The crude peptide is dissolved in 100 mL of 1 M acetic acid and the solution is then evaporated under reduced pressure. The crude peptide is dissolved in a minimum volume of methanol/water 1/1 and triturated with 10 volumes of ethyl acetate.

The triturated peptide is applied to a column (9.4 mm I.D. x 50 cm) of octadecylsilane-silica (Whatman Partisil 10 ODS-2 M 9). The peptide is eluted with a linear gradient of 20-80% of 20/80 0.1% trifluoroacetic acid/acetonitrile in 0.1% trifluoroacetic acid in water. Fractions are examined by TLC and analytical

high performance liquid chromatography (HPLC) and pooled to give maximum purity. Lyophilization of the solution from water gives 77 mg of the product as a white fluffy powder.

Other compounds can be prepared as above and tested for effectiveness as agonists or antagonists in the following test program.

Phase 1 - 3T3 Peptide Stimulated [^{3}H] Thymidine Uptake Assay

Cell Culture. Stock cultures of Swiss 3T3 cells (American Type Culture Collection No. CCL 92) are grown in Dulbecco's Modified Eagles Medium (DMEM) supplemented with 10% fetal calf serum in humidified atmosphere of 10% CO_2/90% air at 37°C. For experimental use, the cells are seeded into 24-well cluster trays and used four days after the last change of medium. The cells are arrested in the G1/G0 phase of the cell cycle by changing to serum-free DMEM 24 hours prior to the thymidine uptake assay.

Assay of DNA Synthesis. The cells are washed twice with 1ml aliquots of DMEM (-serum) then incubated with DMEM (-serum), 0.5μM [methyl-^{3}H] thymidine (20Ci/mmole, New England Nuclear), bombesin (1nM), and four concentrations of the test compounds (1, 10, 100, 1000nM) in a final volume of 0.5ml. After 28 hours at 37°C, [methyl-^{3}H] thymidine incorporation into acid-insoluble pools is assayed as follows. The cells are washed twice with ice-cold 0.9% NaCl (1ml aliquots), and acid soluble radioactivity is removed by a 30 min. (4°C) incubation with 5% trichloroacetic acid (TCA). The cultures are then washed once (1ml) with 95% ethanol and solubilized by a 30 min. incubation (1ml) with 0.1N NaOH. The solubilized material is transferred to vials containing 15ml ScintA (Packard), and the radioactivity

is determined by liquid scintillation spectrometry.

Phase 2 - Small Cell Carcinoma (SCLC) - Bombesin Stimulated [^{3}H] Thymidine Uptake Assay

Cell Culture. Cultures of the human cell carcinoma cell line (NCI-H69) (obtained from the American Type Culture Association) are maintained in RPMI 1640 medium supplemented with 10% fetal calf serum in 10% CO_2/90% air at 37°C. Twenty-four hours prior to assay, the cells are washed with serum-free medium and seeded in 24-well cluster trays.

Assay of DNA Synthesis. Bombesin (1nM), 0.5µM [methyl-^{3}H] thymidine (20 Ci/mmole, New England Nuclear), and four concentrations of the test compounds (1, 10, 100, 1000nM) are added to the cultures to achieve a final volume of 0.5 ml. After a 28 hr incubation at 37°C, the cells are collected onto GF/B glass fiber filters, and the DNA is precipitated with ice-cold TCA. [^{3}H] thymidine incorporation into acid-insoluble fractions of DNA is determined by liquid scintillation spectrometry.

Phase 3 - Peptide-Induced Pancreatitis

Male, Sprague-Dawley rats (250g) are used for these experiments. The test compound, or 0.9% NaCl is administered s.c. 15 min. prior to the bombesin injection. Bombesin injections are given s.c. at a dose of 10 µg/kg, and blood samples are obtained at 1 hr.30 min., 3hr. and 6hr. Plasma amylase concentration are determined by the Pantrak Amylase test.

Phase 4- In Vitro Inhibition of [^{125}I] Gastrin Releasing Peptide (GRP) Binding to Bombesin Receptors

Membranes from various tissues (rat brain, rat pancreas, rat anterior pituitary, SCLC, 3T3 cells) are prepared by homogenization in 50mM TrisHCl containing

0.1% bovine serum albumin and 0.1mg/ml bacitracin followed by two centrifugations (39,000xgx15 min., 4°C) with an intermediate resuspension in fresh buffer. For assay, aliquots (0.8ml) are incubated with 0.5nM [^{125}I]GRP ('2000 Ci/mmol, Amersham Corp.) and various concentrations of the test compounds in a final volume of 0.5ml. After a 30 minute incubation at 4°C, the binding reaction is terminated by rapid filtration through Whatman GF/C filters that have been pre-soaked in 0.3% aqueous polethyleneimine to reduce the level of nonspecific binding. The filters and tubes are washed three times with 4ml aliquots of ice-cold buffer, and the radioactivity trapped on the filters is counted by gamma-spectrometry. Specific binding is defined as the total [^{125}I]GRP bound minus that bound in the presence of 1000nM bombesin.

Phase 5- Inhibition of Gastrin Release

The stomachs of anesthetized rats are perfused with saline collected over 15 minute periods via pyloric cannulation while the test peptide is infused through the femoral vein for periods between 0 and 150 minutes.

Results of Tests of Test Peptides

A number of analogs of bombesin, each containing a non-peptide bond, were synthesized and tested in one or more of the above-described Phase 1 - 5 assays; the results of Phase 1, 2, and 4 tests are given in Table 1 attached hereto (analogs of bombesin are indicated by the symbol "BN"). Brain and 3T3 GRP receptor and thymidine uptake data are expressed in IC50 (nM). Table 1 also gives results for non-peptide bond-containing analogs of three other naturally-occurring peptides, Substance P (which plays a role in the sensation of pain), Neuromedin C, whose C-terminal seven amino acids are similar to those of

bombesin, and litorin, whose eight C-terminal amino acids are identical to Bombesin, with the exception of a Phe substitution for Leu at position A^{13} of bombesin.

In Table 1, the position of the non-peptide bond is indicated by the position of the symbol ψ; i.e., ψ is always shown preceding the amino acid which, in that peptide, is bonded to the amino acid N-terminal to it via the non-peptide bond. Where no amino acid is specified under "structure", as in BIM-26034, the non-peptide bond links the two peptides represented by the numbers given as post-scripts (e.g., between amino acids 7 and 8 of BIM-26034, which otherwise is identical to naturally occurring bombesin).

In Table 1, it can be seen that a preferred placement of the non-peptide bond in bombesin analogs is at the 13-14 position; two of the most active analogs (as indicated by a low GRP receptor IC50 value) are BIM-26027 and BIM-26028. However, BIM-26027 causes proliferation of cancer cells (see Table 1, under thymidine uptake), and therefore is an agonist and not an antagonist. In general, compounds having the non-peptide bond at any position other than the active site of the peptide are agonists rather than antagonists. Table I also shows that when statine replaces the A^{13} and A^{14} residues of bombesin, the resultant bombesin analog BIM-26096 causes proliferation of cancer cells and is therefore an agonist. Bombesin superagonists may be useful in cancer therapy, as suggested by Alexander et al., 1988, Cancer Research 48: 1439-1441, and Alexander et al., 1988, Pancreas 3:297-302, hereby incorporated by reference. Alexander et al. show that chronic bombesin treatment inhibited the growth of human ductal adenocarcinoma transplanted

into athymic mice. These results were surprising for bombesin stimulates growth of normal pancreas tissue. The demonstration of both stimulatory and inhibitory activity suggests that bombesin interacts differently in normal and neoplastic pancreatic tissues.

These observations prompted us to evaluate the affect of BIM-26096, a bombesin analogue which has bombesin-like agonist activity, on the in vitro growth of a pancreatic tumor cell line (AR42J). For these experiments, AR42J cells were subcultured into a 24-well culture plate in Dulbecco's modified Eagle's medium containing 10% fetal calf serum containing various concentrations (0.1-100nM) of BIM-26096. After a 36 hr incubation the cells were removed with a trypsin/EDTA solution and the number of cells were determined using a Coulter Counter. The results are shown below:

Treatment	Cell Count (% Control)
control	100
BIM-26096 (0.1 nM)	78
BIM-26096 (1.0 nM)	73
BIM-26096 (10 nM)	56
BIM-26096 (100 nM)	52

These results indicate that the bombesin agonist, BIM-26096, has in vitro antiproliferative activity against the AR42J rat pancreas tumor.

Finally, Table 1 also shows that bond placement, while important, is not the only factor influencing antagonist activity, and that amino acid substitutions at some positions exert influence as well; this is illustrated by BIM-26030, with Gly in position 11, which exhibited no antagonist activity. Table 1 also gives negative results for analogs of Spantide ([D-Arg', D-Trp^{7,9}, Leu"] Substance P, and Bombesin. Thus the non-peptide bond placement guidelines given

herein should be used in conjunction with the routine assays described above to select useful antagonists or agonists.

In a phase 5 assay, above, the results of which are not given in Table 1, BIM-26028 was shown to be a potent inhibitor of bombesin - stimulated gastric acid secretion.

Use

The peptides of the invention may be administered to a mammal, particularly a human, in one of the traditional modes (e.g., orally, parenterally, transdermally, or transmucosally), in a sustained release formulation using a biodegradable biocompatible polymer, or by on-site delivery (e.g., in the case of anti-cancer bombesin to the lungs) using micelles, gels and liposomes.

The bombesin antagonists and agonists of the invention are suitable for the treatment of all forms of cancer where bombesin-related substances act as autocrine or paracrine mitotic agents, particularly small-cell lung carcinoma. The peptides can also be used for the inhibition of gastric acid secretion, the symptomatic relief and/or treatment of exocrine pancreatic adenocarcinoma, and the restoration of appetite to cachexic patients. The peptides can be administered to a human patient in a dosage of 0.5 μg/kg/day to 5 mg/kg/day. For some forms of cancer, e.g., small cell lung carcinoma, the preferred dosage for curative treatment is 250mg/patient/day.

Other Embodiments

Other embodiments are within the following claims.

For example, as is mentioned above, there are a number of other peptide families from which agonists or antagonists can be made according to the invention. Some of these families are substance P and related peptides, vasoactive inestial peptide (VIP) and related peptides, and neurotensin and related peptides. The number of peptides in each family on which antagonists or agonists can be based is large. For example, there are at least 10 currently-known peptides in the VIP family, including sauvagine and urotensin. In addition, there have been isolated seven natural bradykinin-like peptides. Neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH) has two peptide bonds which advantageously can be replaced by non-peptide bonds: Ile-Leu and Tyr-Ile. In addition, neurotensin antagonists can be missing any or all of the N-terminal seven amino acid residues, as it has been shown (Granier et al. (1984) Eur. J. Biochem. 124: 117) that they are not needed for biological activity and binding. Screening of neurotensin antagonists can be by binding to SCLC receptors. Gastrin releasing peptides (GRP) and related peptides (e.g., Neuromedin C (GRP 18-27)) have a bond between amino acid residues 13 and 14 which can be replaced with a non-peptide bond to form a GRP antagonist.

Table 1

Code	Structure	Brain GRP Receptor IC50(nM)	3T3 GRP Receptor IC50(nM)	Thym. Uptake IC50(nM)
BIM-26025	[$His^{12}\Psi[CH_2NH]Leu^{14}$]BN	>1000		
BIM-26026	[$Ala^{9}\Psi[CH_2NH]Leu^{14}$]BN	>1000		1574
BIM-26027	[$Val^{10}\Psi[CH_2NH]Leu^{14}$]BN	0.48	2.3	agonsit EC50=0.07n M
BIM-26028	[$Leu^{13}\Psi[CH_2NH]Leu^{14}$]BN	13		14.7
BIM-26030	[$Gly^{11}\Psi[CH_2NH]Leu^{14}$]BN	>1000		
BIM-26034	[$\Psi[CH_2NH]^{8,7}$]BN	>1000		
BIM-26036	[Des-$pGlu^{1}$,Gln^{2},Ψ(Ala^{9}, Val^{10})Phe^{12}]BN	>1000		
BIM-26046	[$Gly^{11}\Psi[CH_2NH]$D-Phe^{12}, Leu^{14}]BN	>1000		
BIM-26048	[D-$Phe^{12}\Psi[Ch_2NH]Leu^{13}$, Leu^{14}]BN	>1000		
BIM-26056	[$Leu^{10}\Psi[CH_2NH]$ $Leu^{11}NH_2$]Substance P	>1000		
BIM-26057	[Cys^{9},ψLeu^{13},Cys^{14}]BN	>1000		

Code	Structure	Brain GRP Receptor IC50(nM)	3T3 GRP Receptor IC50(nM)	Thym. Uptake IC50(nM)
BIM-26061	[D-pGlu,D-Ala^5,ΨLeu^7, Met^8]BN	>1000		
BIM-26062	[ΨPhe^{13},Leu^{14}]BN	>1000		437
BIM-26063	[des-Glu^7,ΨLeu$^{13-14}$]BN	>1000		
BIM-26064	[ψLeu^{10},Nle^{11}]Spantide	>1000		
BIM-26067	[des-Gln^7,ψLeu$^{13-14}$]BN	>1000		
BIM-26068	[ψLeu^{13},Phe^{14}]BN	2.9		70
BIM-26070	[ψD-Trp^9,Nle^{11}]Spantide	>1000		
BIM-26071	[Tyr^4,ψLeu^{13} [CH_2NH]-Met^{14}]BN	34	16	104
BIM-26072	[Cys^9,Leu^{13}[CH_2NH] Cys^{14}]BN	>1000		
BIM-26073	[Cys^9,ψLeu^{13}[CH_2NH] Cys^{14}]BN	>1000		
BIM-26074	[Des-Gln^7,ψLeu^{13}[CH_2NH] Leu^{14}]BN	>1000		
BIM-26075	[D-Phe^{11},ψLeu$^{13-14}$]BN	>1000		

Code	Structure	Brain GRP Receptor IC50(nM)	3T3 GRP Receptor IC50(nM)	Thym. Uptake IC50(nM)
BIM-26076	[D-Phe^{11},ψLeu$^{13-14}$]BN	>1000		
BIM-26077	[D-Ala^{5},ψLeu$^{13-14}$]BN	517	196	1001
BIM-26078	[D-Ala^{11},ψLeu$^{13-14}$]BN	>1000		70
BIM-26079	[ψPhe^{7},Leu^{11}]Spantide	>1000		
BIM-26080	[ψGln^{6}-Nle^{11}]Spantide	>1000		
BIM-26081	[ψD-Trp^{7}-Nle^{11}]Spantide	>1000		
BIM-26082	[ψPhe^{8}-Nle^{11}]Spantide	>1000		
BIM-26083	[ψGLn^{6}-Nle^{11}]Spantide	>1000		
BIM-26084	[ψD-Trp^{7}-Nle^{11}]Spantide	>1000		
BIM-26085	[ψPhe^{8}-Nle^{11}]Spantide	>1000		
BIM-26086	[D-Phe^{12},ψLeu[CH_2NH]Leu^{14}]BN	>1000		
BIM-26088	[ψGly^{9}[CH_2NH]Leu^{14}]Spantide	>1000		
BIM-26089	[ψGln^{6}[CH_2NH]Leu^{11}]Spantide	>1000		
BIM-26090	[ΥPhe^{7},Leu^{11}]Substance P			>1000

Code	Structure	Brain GRP Receptor IC50(nM)	3T3 GRP Receptor IC50(nM)	Thym. Uptake IC50(nM)
BIM-26091	[ψPhe^{8},Leu^{11}]Substance P			>1000
BIM-26092	[ψLeu^{9}]Neuromedin C		242	466
BIM-26093	[D-Ala^{1},ψ[CH_2NH]Leu^{9}] Neuromedin C		82	171
BIM-26094	[D-Ala^{5,11},Leu^{13}ψ[CH_2NH] Leu^{14}]BN		1613	574
BIM-26095	[D-Ala^{6},Leu^{9}ψ[CH_2NH] Leu^{10}]Litorin		2623	1209
BIM-26096	[Sta^{13},Des Met^{14}]BN	33		agonsit EC50=3nM
BIM-26097	[Ac-Lys^{7},ψLeu^{13}]BN_{7-14}	1000		>1000
BIM-26098	[Lys^{7},ψLeu^{13}]BN_{7-14}	1000		
BIM-26099	[ψLeu^{13},Met]BN		73	78
BIM-26100	[Phe^{8}ψ[CH_2NH]Leu^{9}]Litorin		74	22
BIM-26101	Leu^{8}ψ[CH_2NH]Leu^{9}]Litorin		17.9	257
BIM-26102	ψPhe^{9}[CH_2NH]Met^{10}NH_2 Neuromedin ß		184	>1000

Code	Structure	Brain GRP Receptor IC50(nM)	3T3 GRP Receptor IC50(nM)	Thym. Uptake IC50(nM)
BIM-26103	ψLeu^{13}[CH_2NH]Met^{14}NH2 A-Lytensin		>1000	>1000
BIM-26104	ψLeu^{7}[CH_2NH]Met^{8}NH_2 GRP(20-27)			>1000
Spantide	[D-Arg^{1},D-Trp^{7,9},Leu^{11}] Substance P		3303	2171
Bombesin	pGlu-Gln-Arg-Leu-Gly-Asn-Gin-Trp-Ala-Val-Gly-His-Leu-Met-NH_2	15	0.17	

Claims

1. A linear peptide which is an analog of naturally occurring, biologically active bombesin having an active site and a binding site responsible for the binding of bombesin to a receptor on a target cell, cleavage of a peptide bond in said active site of said naturally occurring bombesin being unnecessary for in vivo biological activity of bombesin, said analog having a non-peptide bond instead of a peptide bond between an amino acid of said active site and an adjacent amino acid, said analog being capable of binding to said receptor, so that said analog is capable of acting as a competitive inhibitor of said naturally occurring peptide by binding to said receptor and, by virtue of said non-peptide bond, failing to exhibit the in vivo activity of said naturally occurring bombesin.

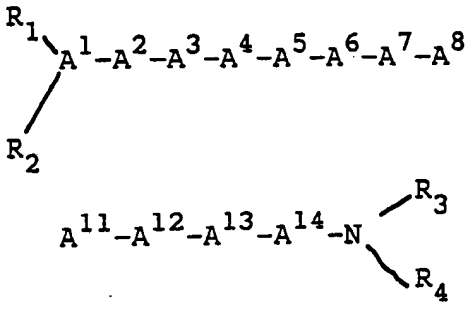
2. The linear peptide of claim 1 wherein said naturally occurring bombesin is characterized in that one or more amino acids in the amino terminal half of bombesin are hydrogen bonded to one or more amino acids in the carboxy terminal half of bombesin, and said non-peptide bond of said linear peptide decreases said hydrogen bonding.

3. The linear peptide of claim 2 wherein said hydrogen bonded amino acids of said naturally occurring bombesin make up at least a portion of the active site of said naturally occurring bombesin, so that said active site is inactivated by the decrease in hydrogen bonding caused by said non-peptide bond.

4. A linear peptide which is an analog of naturally occurring, biologically active human bombesin which includes an active site comprising at least one amino acid in the carboxy terminal half of bombesin, said linear peptide including said amino acid in its carboxy terminal half, there being a non-peptide bond bonding said amino acid to an adjacent amino acid.

5. The linear peptide of claim 4 wherein said amino acid of said naturally occurring bombesin is hydrogen bonded to another, non-adjacent amino acid in said bombesin, and said non-peptide bond in said linear peptide causes a decrease in said hydrogen bonding which inactivates said bombesin.

6. An effective bombesin antagonistic peptide containing the amino acid formula:



wherein

A^1 = pGlu or is deleted;

A^2 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, ß-naphthylalanine or is deleted;

A^3 = Arg, D-Arg, Lys, D-Lys or is deleted;

A^4 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, ß-naphthylalanine or is deleted ;

A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, D-Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, ß-naphthylalanine, D-Ala or is deleted;

A^6 = Gln, Asn, Gly, Ala, D-Ala, N-Ac-D-Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, p-Glu, ß-naphthylalanine or is deleted;

A^7 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, D-Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, His, or ß-naphthylalanine;

A^8 = Trp;

A^9 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, or B-naphthylalanine;

A^{10} = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, or ß-naphthylalanine;

A^{11} = Gly, or D-Ala;

A^{12} = His, Phe, or p-X-Phe (X = F, Cl, Br, OH, CH_3);

A^{13} = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, or ß-naphthylalanine;

A^{14} = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, Phe, p-X-Phe (X = F, Cl, Br, OH or CH_3), Trp, or ß-naphthylalanine;

provided that

each R_1, R_2, R_3, and R_4, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, COE_1 (where

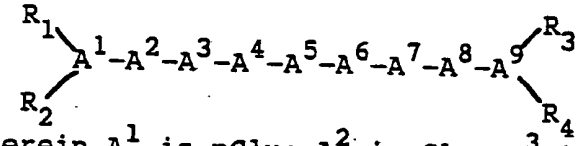
E_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or $COOE_2$ (where E_2 is C_{1-10} alkyl or C_{7-10} phenylalkyl), and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide, which can be A^1, A^2, A^3, A^4, A^5, A^6, or A^7, and further provided that when one of R_1 or R_2 is COE_1 or $COOE_2$, the other must be H, and when one of R_3 or R_4 is COE_1 or $COOE_2$, the other must be H, and further provided that when A^1 = pGlu, R_1 must be H and R_2 must be the portion of Glu that forms the imine ring in pGlu; and for each of the residues A^7, A^8, A^9, A^{10}, A^{11}, A^{12}, and A^{13}, independently, the carbon atom participating in the amide bond between that residue and the nitrogen atom of the alpha amino group of the adjacent amino acid residue may be a carbonyl carbon or may be reduced to a methylene carbon, provided that at least one such carbon atom must be reduced to a methylene carbon; or a pharmaceutically acceptable salt thereof.

7. The effective bombesin antagonist peptide of claim 6 wherein A^1 through A^6 are deleted and the carbon atom participating in the amide bond between Leu^{13} and Leu^{14} is a methylene carbon; or a pharmaceutically acceptable salt thereof.

8. The effective bombesin antagonist peptide of claim 6 wherein, for each of said residues A^{11}, A^{12}, and A^{13}, independently, the carbon atom participating in the amide bond between that residue and the nitrogen atom of the alpha amino group of the adjacent amino acid residue may be a carbonyl carbon or may be reduced to a methylene carbon, provided that at least one such carbon atom must be reduced to a

methylene carbon; or a pharmaceutically acceptable salt thereof.

9. An effective litorin antagonist peptide containing the amino acid formula:



wherein A^1 is pGlu; A^2 is Gln; A^3 is Trp; A^4 is Ala; A^5 is Val; A^6 is Gly or D-Ala; A^7 is His; A^8 is Phe or Leu; and A^9 is Met or Leu; provided that the carbon atom participating in the amide bond between the A^8 residue and the nitrogen atom of the alpha amino group of the adjacent amino acid residue may be a carbonyl carbon or may be reduced to a methylene carbon; or a pharmaceutically acceptable salt thereof.

10. An effective bombesin agonist of the general formula of claim 6 wherein, for each of the residues A^9, A^{10}, A^{11}, A^{12}, A^{13}, and A^{14}, independently, the carbon atom participating in the amide bond between that residue and the nitrogen atom of the alpha amino group of the adjacent amino acid residue may be a carbonyl carbon or may be a non-peptide bond, provided that said non-peptide bond is said carbonyl carbon having been reduced to a methylene carbon, further provided that at least one such carbon atom must be reduced to a methylene carbon; or a pharmaceutically acceptable salt thereof.

11. A bombesin agonist having the amino acid formula

pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Leu[$Val^{10}\Psi[CH_2NH]Leu^{14}$]BN.

12. An effective bombesin agonist having the amino acid formula of claim 6 which is an analog of naturally occurring, biologically active bombesin having an active site, said active site includes the positions A^9, A^{10}, A^{11}, A^{12}, A^{13}, and A^{14}, and a binding site responsible for the binding of said bombesin to a receptor on a target cell, said analog having either (a) said non-peptide bond at residues other than within said active site, or (b) having at least one statine or AHPPA residue in place of two naturally occurring amino acids of said active site, and further provided that the peptide can contain statine or AHPPA when all bonds between amino acid residues are peptide bonds, and further provided that when an amino acid residue is statine or AHPPA, the amino acid to the right of it in the formula is deleted, so that said analog is capable of binding to said receptor, and, by virtue of said statine or AHPPA residue, exhibiting enhanced in vivo biological activity compared to said naturally occurring bombesin.

13. A bombesin agonist having the amino acid formula

pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-[Sta^{13},Des Met^{14}].

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03286

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): C07K 7/02, 7/06, 7/08
U.S. CL: 530/327, 328, 323

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	530/327, 328, 323

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Chemical Abstracts and Biological Abstracts Online Computer Search.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, A, 4,207,311 (Brown et. al.), 10, June 1980. See column 2, line 29 in particular.	9
A	Am J. of Physiol, (Maryland, USA) issued 1986, (Heinz-Erian et. al.), "[D-Phe12] bombesin analogues: a new class of bombesin receptor antagonists", pages G439-G442.	1-13
A	Proc. Natl. Acad. Sci. USA (Washington, D.C., USA) volume 82, issued November, 1985. (Zachary et. al.), "High-affinity receptors for peptides of the bombesin family in Swiss 3T3 cells", pages 7616-7620.	1-13

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22 December 1988	16 FEB 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Christina Chan Christina Chan

Form PCT/ISA/210 (second sheet) (Rev.11-87)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
A	J. Med. Chem. (Washington, D.C., USA) volume 28 issued 1985, (Martinez et. al.), "synthesis and biological activities of some pseudo-peptide analogues of tetragastrin: The importance of the peptide backbone", pages 1874-1879.	1-13
A	J. Med. Chem. (Washington, D.C., USA) volume 30, issued 1987, (Rodriguez et. al.). "Synthesis and biological activities of Pseudopeptide analogues of the C-terminal heptapeptide of cholecystokinin. On the importance of the peptide bonds", pages 1366-1373.	1-13
Y	J. Med. Chem. (Washington, D.C. USA) volume, 30, issued 1987, (Sasaki et. al.), "Solid-Phase Synthesis and biological Properties of [CH_2NH] Pseudopeptide analogues of a highly potent somatostatin octapeptide", pages 1162-1166. See pages 1162, 1164, 1166 in particular.	1-8 10-13
Y	Cancer Surveys (Oxford, England) volume 4, No. 4, issued 1985 (Cuttitta et. al.), "Autocrine growth factors in human small cell lung cancer", pages 707-727. See page 718 in particular.	1-8 10-13
X,P	Chemical Abstract, (Columbus, Ohio, USA) volume 109, issued 1988, (Coy et. al.), "Probing peptide backbone function in bombesin. A reduced peptide bond analog with potent and specific receptor antagonist activity", the abstract No. 32216K, J. Biol. Chem. 1988, 263 (11), 5056-60 (Eng).	1-8 10-13